

# Focus On High Potency Manufacturing

## Executive Q&A



**Charlie Johnson,**  
Head of High Potency  
Business Unit —  
CARBOGEN AMCIS

MAIN IMAGE: CARBOGEN AMCIS High Potency manufacturing area in Bubendorf, Switzerland.

*In line with this edition's scheduled Focus on High Potency Manufacturing, I decided to interview Charlie Johnson, Head of High Potency Business Unit, at CARBOGEN AMCIS, a Dishman Group company, offering drug substance development and commercialisation services to the (bio)pharmaceutical industry at all stages of drug substance development. After the recent announcement of the Swiss operations restructuring, 2011 has so far proved to be a year of consolidation for the company's high potency portfolio. Charlie Johnson talked about the recent developments in the company's High Potency business, the successful containment performance qualification of the high containment multi-purpose facility in India and its global presence in the API manufacturing market.*

Elizabeth Valero, Editor.

Last February, CARBOGEN AMCIS announced a plan to restructure the Swiss operations in Bubendorf, Aarau and Hunzenschwil (Neuland) to adapt the company to a changing market situation; can you give me a brief overview of the transition that the company is currently undergoing, highlighting the key elements of the business that have changed or been introduced?

After the internal and public announcements, the company management went through the plans with the departmental heads and finalised the business process improvements and the resulting restructuring consequences. The key measures are directed at focusing and simplifying the customer interaction process by empowering the project leaders and thus bringing them closer to the customer. Also, the number of sales personnel was increased to allow better customer interactions.

At the same time, the company allocated funds to innovate its service portfolio and allocated 10+ resources to exclusively work in these fields.

One key aspect is that we have looked at where we do which activities and focused certain activities in one place. In other areas, where flexibility and demand warrant it, processes are introduced to allow additional capacity to become available, for example, in the Hunzenschwil (Neuland) site, laboratory space is converted to allow for high potency category 3 work



(1–100 µg/m<sup>3</sup>), where we see increased customer demand. In December, CARBOGEN AMCIS AG completed new stability chambers and expanded its analytical service portfolio by introducing new solid state and pre-formulation services to cover both drug products and drug substances. Other new services and capacity enhancements are in the pipeline and will be communicated when operational.

**So the company focus remains on API substance development and manufacture, with a main focus on high potency and drug conjugates; can you give me breakdown of the high potency services and capabilities at the company?**

The focus for the High Potency Business is and will remain development, commercialisation and manufacturing of oncology products, dictated by continuing strong market investment in this area. Services cover R&D, including route selection and process development to support rapid supply of API for GLP<sup>(1)</sup> and FIM<sup>(2)</sup> studies. Follow-on clinical supplies and preparation for commercialisation of processes for routine manufacturing is our core activity. Commercialisation is based on the QbD<sup>(3)</sup> approach, increasingly requested by clients and regulators (FDA and EMA<sup>(4)</sup>) alike. Commercial manufacturing and supply chain management are also core activities.

Three commercial products are currently manufactured in Switzerland with a further two in late commercialisation. Commercial products migrate to larger scale facilities in India or China as dictated by product growth and specific supply chain requirements, for example, risk mitigation, economics and market access requirements. Development and commercialisation of high potency products is backed by extensive in-house analytical capabilities from dedicated laboratories. Dedication of analytical activities has been an industry leading commitment to ensure appropriate controls are maintained for high-throughput project development and manufacturing.

**I understand the company recently invested in new filter dryers and wet milling equipment at the Bubendorf site; how have these enhanced overall manufacturing capability and capacity in the large-volume production facility?**

Yes, we have invested in a second filter-dryer for our dedicated High Potency Pilot Facility to increase throughput

for clinical phase projects and increase operational productivity for smaller scale commercial products. A major impact has been to improve competitiveness in the market for early phase development projects. Wet milling has been developed in-house as a preferred alternative to dry milling, for example, jet-milling. Wet milling brings several advantages when working with highly potent compounds that reduce the overall exposure potential of the particle sizing operation. The key advantages are one — working with more dilute process streams, two — avoidance of dusty solids, three — higher recovery rates and four — low capital cost compared with dry-milling. Wet milling is not a complete substitution for dry milling in all cases, but is preferred when desired parameters allow. Since investing in lab and production equipment 12 months ago, the capabilities have been in significant demand and could be offered as a standalone service, although they are currently mainly associated with full service manufacturing projects. We are also investigating flow cell sonication milling to further compliment our capabilities for low micron PSD<sup>(5)</sup> requirements.

**In 2009 and 2010, the company announced two strategic partnerships for the drug products' development and manufacturing with EirGen and NextPharma. Can you explain why and the advantages these offer to your customers?**

As compression of clinical timelines and streamlining of services become ever more important aspects in drug development, there is a clear industry trend towards having more integrated API/formulated product offerings available. Historically, CMOs for API and formulation have largely remained separate with relatively few service providers specialising in both capabilities under one organisation/geographical location.

Through strategic API/dosage form partnership initiatives, CARBOGEN AMCIS and its partners are offering a high level of integration that can accelerate availability of drug product for use in the clinic. By carefully coordinating drug substance development, manufacturing and supply of API to the formulation partner, timelines can be accelerated and manufacturing schedules optimised. Additionally, the burden of project management for our client is reduced as a single point of project coordination removes the need for management of multiple interfaces. Overlap of certain

functional activities — such as analytics — is also of benefit, reducing duplication of effort in terms of analytical development for example, leading to time and cost savings.

**How do these partnerships integrate with or complement CARBOGEN AMCIS' services and the recent investments in new stability chambers and solid state services for pre-formulation studies?**

Again, synchronisation of stability programmes for drug substance and drug product boosts efficiency and reduces cost for our clients. For example, CARBOGEN AMCIS may undertake development and validation of analytical methods for both drug substance and drug product and thereby represent a single point of analytical release and stability testing for both drug substance and drug product. Investment in stability chambers gives greater capacity in this respect.

In terms of pre-formulation studies, this is more important for our collaboration on solid orals dosage forms. CARBOGEN AMCIS has invested in pre-formulation equipment to assess physico-chemical relationships, for example, DVS<sup>(6)</sup>, SSA<sup>(7)</sup> and water activity, flowability and compressibility. These are all important physical characteristics impacting the formulation options for solid dosage forms. In addition, we have invested in equipment to determine dissolution and disintegration kinetics. Being able to provide a basic pre-formulation data set allows our partner Eirgen to more quickly select and evaluate formulation options such as selection of excipients, feasibility for direct microdosing and environmental controls needed during the formulation process.

**Perhaps the most important CARBOGEN AMCIS announcement this year is the most recent, the new High Potency Facility in India, which has just received containment performance qualification according to ISPE's SMEPAC<sup>(8)</sup> guideline; what does this conformance mean for customers?**

Our new, commercial-scale High Potency Facility has recently passed an independent evaluation of containment performance of all critical isolation equipment. The evaluation was conducted according to the recognised industry standard SMEPAC guideline. The results of the testing confirm that the facility operates within its design qualification at Occupational Exposure Levels of < 1µg/m<sup>3</sup> (8hr TWA<sup>(9)</sup>). This is essential for maintenance of a safe operating environment for the



**FAR LEFT: CARBOGEN AMCIS large-scale High Potency Facility, located on the site of Dishman Pharmaceuticals and Chemicals Ltd., Ahmedabad, India.**

**LEFT: CARBOGEN AMCIS' new stability chambers at the Hunzenschwil (Neuland), Switzerland site.**

**RIGHT: CARBOGEN AMCIS High Potency Process R&D Laboratory, Bubendorf, Switzerland.**



workforce and gives our customers confidence that they are working with a partner committed to the welfare of its workforce and the wider environment. The containment levels achieved ensure that the new facility is capable of working with Category IV materials, those requiring the most stringent containment controls, for example, Category 1 IARC<sup>(10)</sup> carcinogens, and those possessing therapeutic activity at sub mg levels. Proof of this level of containment performance is also very important to our clients, many of whom operate similar facilities in the US and Europe and expect equivalent levels of containment control.

#### What are the capabilities offered by the new facility in India?

The facility is a commercial-scale offering for highly potent APIs. The main role of the facility is to support launch and manufacture of innovator NCEs<sup>(11)</sup> and to enable lifecycle management for commercial products from the Swiss manufacturing operations. The facility provides larger scale manufacturing capacity, especially for the newer class of oral cytostatic agents.

Initial investment of USD 20M has enabled a standalone High Potency Facility that includes development and manufacturing support labs dedicated QC and QA infrastructure, two fully segregated manufacturing cells and wet and dry milling capabilities — all under one roof. All services — power (including back-up generators), air handling units, utilities and waste — are likewise dedicated to the facility.

The facility can handle Category IV compounds < 1 µg/m<sup>3</sup> OEL in batch sizes up to 150 kg. Annual production volumes for the initial investment is in the range 5 to 6 MTes p.a. The facility has been designed for expansion within a short timeframe; two larger manufacturing cells can be operational within a 12 month horizon and will add a further 10 MTes of annual capacity.

**CARBOGEN AMCIS is committed to the constant improvement of existing risk assessment procedures to ensure safety of workers and cGMP product quality. How important is this to your customers and how do you ensure the safe handling of a NCE in the development stage for which limited data is available?**

Both aspects of worker safety and GMP are of fundamental

importance and both rely on toxicological considerations for the compounds in question. The GMP aspects are probably of greater interest to our clients as they have the potential to impact the patients.

NCEs early in development naturally demand a more conservative approach as reliable data on which to base occupational exposure decisions and allowable carryover limits is more limited. Our risk assessment procedures are rigorous, anticipating MoA<sup>(12)</sup>, hazards associated with known classes of compounds, available animal Tox information, SAR<sup>(13)</sup> methodology and known genotoxic alert structures. We also take into consideration our clients' perspectives and that of external risk assessment agencies where available to build up an aggregate assessment of inherent risks for each API and its intermediates.

A recent development in this area has been the issuance of ISPE's RiskMapp guide that has brought together in one place the perspectives of industry and regulators alike on the management of carry-over risks in multi-product GMP facilities. CARBOGEN AMCIS has reviewed this guidance in the context of its own procedures and policies and has concluded that its risk assessment procedure and methodology is broadly in line with RiskMapp<sup>(14)</sup>. There are some key similarities, for example, the modification of MACO<sup>(15)</sup> limits by taking into account the TTC<sup>(16)</sup> in relevant circumstances where genotoxicity is either known or suspected. This typically promotes more stringent MACOs/ADEs<sup>(17)</sup> and associated cleaning limits and is a good example of a conservative approach in the absence of hard data.

#### How do you integrate CARBOGEN AMCIS' offering with the Dishman service portfolio?

CARBOGEN AMCIS and the parent Dishman have a diverse set of assets for development and manufacturing of highly potent compounds across Switzerland, India and China. Typically, early PRD<sup>(18)</sup> and clinical supplies for NCE projects are undertaken in Switzerland where significant expertise and experience has been built up over the last 10 years. Problem solving, speed and excellent project management are the key success factors at this stage.

Likewise, the technical aspects of commercialisation for late clinical phase products is usually undertaken in Switzerland, for example, process optimisation, validation and analytical validation. Commercialisation is very much centred on the

principles of QbD as incorporated in ICH<sup>(19)</sup> Q8, 9 and 10, and again we have much experience with this approach. Supply chain design and risk management are also key aspects of the commercialisation process and this is where our core manufacturing strategy is developed. For example, consideration is given to the requirement of one or more group manufacturing locations for risk management — how will critical starting materials be handled?, external versus internal sourcing or a combination of both. The Dishman group has a large and diverse asset base in India and China, which gives multiple options for supply of upstream (non high potency) intermediates and key starting materials. That means that the groups as a whole are able to offer economical and secure supply chain solutions that many of our competitors cannot access.

#### Having chosen to invest in new HC equipment and a High Potency Facility in India, are we to assume that CARBOGEN AMCIS is predicting a significant increase in demand for high potency manufacturing?

Yes, this is predominantly driven by the continued strong growth in oncology, although in general there is a trend to highly active low dosed APIs in other therapeutic areas as well. We anticipate continued growth and increased outsourcing for highly potent compounds at all scales, but in particular for larger scale capacity in both NCE and generic sectors. The group has invested ahead of the curve and is now well placed to take advantage of these opportunities.

**CARBOGEN AMCIS**  
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#### Footnotes:

(1)GLP = Good Laboratory Practice (2)FIM = First in Man (3)QbD = Quality by Design (4)EMA = European Medicines Agency (5)PSD = Particle Size Distribution (6)DVS = Dynamic Vapour Sorption (7)SSA = Specific Surface Area (8)SMEPAC = Standardised Measurement of Equipment Particulate Airborne Concentration (9)TWA = Time Weighted Average (10)IARC = International Agency for Research on Cancer (11)NCEs = New Chemical Entities (12)MoA = Mode of Action (13)SAR = Structure Activity Relationship (14)Risk-MaPP = Risk-Based Manufacture of Pharmaceutical Products (15)MACO = Maximum Allowable Carry Over (16)TTC = Threshold of Toxicological Concern (17)ADEs = Acceptable Daily Exposures (18)PRD = Process Research Development (19)ICH = International Conference on Harmonisation